**REMARKS**

Upon entry of the amendments herein, claims 1-28 remain pending in the application. Claims 1, 4 and 22 have been amended to correct informalities, some of which were cited by the Examiner. Claim 13 has been amended to more clearly recite the subject matter regarded as the invention. No new matter has been introduced by any of the amendments.

The Examiner has asserted that the application is deficient because it contains sequence disclosures encompassed by the definitions set forth in 37 CFR §1.821(a)(1) and (a)(2) but no sequence listing has been submitted. In particular, the Examiner cites the sequences found in Table II on page 25 of the specification.

37 CFR §1.821(a) states: "Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. 'Specifically defined' means those amino acids other than 'Xaa'... as defined in accordance with the WIPO Handbook..., including Tables 1 through 6 in Appendix 2...." The sequences in the present application to which the Examiner refers contain no specifically defined amino acids. All of the sequences in Table II of the application consist of units designated either by "P" (polar) or "H" (hydrophobic). Thus, the units of the sequences set forth in Table II are not

specific amino acids; they only designate that the unit is either a member of the class of amino acids with hydrophobic side chains or amino acids with polar side chains. Such designations do not fall within the list of amino acids set forth in Tables 3 and 4 of Appendix 2 of Annex C of the WIPO Handbook. Accordingly, no sequence listing is required for the present application.

Claim 1 has been objected to for containing improper periods. Appropriate correction has been made.

Claim 1, and claims 2-28 dependent therefrom, have been rejected because there is not a literal connection between the phrase "protein backbone configurations" in the preamble of claim 1 and the subsequent recited steps of the method.

The Examiner has requested clarification of the metes and bounds of claim 1. The Examiner's attention is drawn to the second paragraph on page 9 of the specification. Therein is disclosed that a "configuration" in the instantly claimed method refers to a particular spatial arrangement of secondary structural elements having a specified order in which the elements are to be connected by loops. Accordingly, the relationship between the "configurations" of the preamble and the "secondary structural elements" of step (a) is clearly established, and there is no "disconnect" between the claim

preamble and the subsequent steps that renders the claim indefinite as to the metes and bounds. There is no requirement that the terms in the preamble be repeated in the body of the claim, particularly when the teaching is clear as to the connection between the terms in the preamble and those in the subsequent steps.

When one of skill in the art refers to a new protein fold, it is understood that reference is being made to a stack; it is the stack that defines the novelty of a fold. With reference to the disclosure running from page 8, line 10 through page 9, line 20 (which includes the passage cited in the paragraph immediately above), one understands that a configuration is a stack with turns connecting the secondary elements. One further understands that a stack is really the essential component of the configuration and that once the stack has been identified, everything else falls into place. Thus, withdrawal of the rejection of claim 1 set forth in section 6 of the Office Action is warranted and is respectfully requested.

Claims 9, 13, 15 and 20 have been rejected as being vague and indefinite because of the recitation of "step (b)" therein. Amendment herein of the informalities cited by the Examiner in claim 1 renders moot the rejection of these dependent claims and the additional claims dependent therefrom.

Claims 13 and 14 have been rejected for recitation of "predetermined constraint." The Examiner asserts that this causes the claim to be indefinite because it is not clear whether the constraint is predetermined "in the dependent from claim 1 or some other step that has not been specified in the instant claims." In the first place, Applicants wish to point out that claim 13 specifies that the predetermination comes as part of step (b) of claim 1. Therefore it is not seen where the confusion arises. Nonetheless, the claim has been amended herein in an effort to make even clearer how the predetermination of the constraint fits into the scheme of the claimed method.

Claim 22 has been rejected as vague and indefinite for recitation of the acronym "crms." Applicants wish to point out that this term is clearly defined on page 13, line 14 of the specification. Nonetheless, in the interest of expediting prosecution of the application the claim has been amended by addition of the full name for which the acronym stands.

Claims 26-28 have been rejected under 35 USC §112, first paragraph as not being enabled by the specification. In particular, the Examiner asserts that insufficient guidance is provided as to the determination of the $E_{designability}$ recited in these claims. Applicants disagree with this assessment.

Any choice of $h_o$ leads to a particular set of 100 most designable 4-helix stacks. The more positive the value of $h_o$, the more compact will be the stacks in the top 100 and the more negative the value of $h_o$, the less compact will be the stacks. The value of $h_o$ is adjusted so that the top 100 stacks have approximately the same compactness as natural 4-helix bundles. Specifically, to make this comparison of compactness, the percentage surface exposure for a set of natural 4-helix bundles is evaluated. A value of $h_o$ is then determined for which the 100 most designable stacks have a distribution of percentage surface exposures that best matches the distribution of percentage surface exposures of the natural 4-helix bundles. In other words, $h_o$ is chosen so that the two distributions have the smallest $chi^2$ difference. This best fit is shown in Figure 5 of the instant application. Thus, one of skill in the art is provided sufficient information about the determination of $h_o$ to derive $h_i$. It is respectfully requested that this rejection be withdrawn as well.

Claims 1-8, 13-15, 20, 23 and 24 have been rejected under 35 USC §102(b) as anticipated by the cited Science article of Dahiyat et al. (1997). The Examiner has set forth a number of points describing information allegedly provided by Dahiyat and relating this alleged disclosure to various of the rejected

claims. However, all of this notwithstanding, the analysis of patentability can be simplified if one understands that the method of Dahiyat, et al. can only be practiced from a starting point of a predetermined backbone configuration. Dahiyat, et al. provide no method for designing new stable backbone configurations. Rather, they are looking for variant amino acid sequences that stably adopt a predetermined configuration. As the Examiner even acknowledges, Dahiyat teaches the use of a protein library, i.e., a catalog of known proteins, as the starting point for the design method.

More particularly, Dahiyat, et al. describe a procedure wherein they begin with the known backbone configuration of a naturally occurring zinc-finger protein and apply their algorithm to manipulate the protein (by introduction of variant amino acid sequences) to produce a redesigned zinc finger with the exact backbone configuration of the original protein; the significant difference in the redesigned protein is that it is no longer dependent on a zinc ion for stability. The algorithm of Dahiyat thus is used with naturally occurring proteins as the starting point to generate "redesigned" proteins that maintain the exact configurations of the original proteins. This is nothing like the instantly claimed method which affords the designing of novel proteins, whose novelty lies in their

backbone configurations, as well as in their sequences. Accordingly, there is no way that a valid case can be made that the approach of Dahiyat, et al. anticipates the instantly claimed method.

Claims 1-25 have been rejected under 35 USC §103(a) as being obvious over the Dahiyat reference discussed above in combination with U.S. Patent No. 6,403,312 to Dahiyat, et al. Again, the Examiner enumerates a number of separate points of alleged disclosure of the secondary reference purported to apply to specific limitations set forth in specific rejected dependent claims. Whether or not the Examiner's assertions with regard to the disclosure of the secondary reference are valid, the fact remains that these specific disclosures do not make up for the fundamental deficiency in the primary reference that renders it ineffective against the instantly claimed subject matter.

Again, as the Examiner also acknowledges, the secondary Dahiyat references teaches the use of a protein library as the starting point. As the Dahiyat patent discloses at column 5, lines 43 and 44, a "scaffold protein" is defined as a protein for which a secondary library of variants is desired. In the Dahiyat method, the term "scaffold" essentially refers to the backbone configuration of a known protein. The variants of interest to Dahiyat are variants of sequences of amino acids in

a given backbone configuration, not variants of the scaffold or configuration itself. As seen, for example, at the bottom of column 6 of the Dahiyat patent, the term "primary library" refers to a collection of optimized sequences, i.e., variant amino acid sequences for a fixed, known scaffold or backbone. Similarly, the "secondary library" of Dahiyat is a subset of the primary library.

In summary, Dahiyat does not provide a method for finding novel protein backbone configurations. The essence of Dahiyat is finding a new sequence or sequences that conform to a given known configuration that is the starting point. At no stage does Dahiyat disclose generating a set of new configurations. No disclosure is required pertaining to where such a backbone configuration or set of configurations may come from, since Dahiyat relies solely on naturally occurring, or at least predetermined, backbones as a starting point. On the other hand, the essence of the instant invention is the identification of novel backbone configurations.

Accordingly, the combination of the two Dahiyat references cannot be said to render obvious the instantly claimed method.

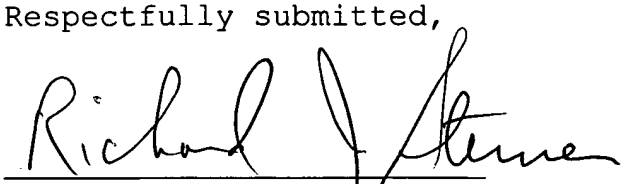
In view of the amendments herein and the arguments set forth above, all outstanding rejections have been overcome and

the application is in conditions for allowance. Reconsideration and allowance of pending claims 1-28 are respectfully requested.

The Commissioner is hereby authorized to charge any fees which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: August 11, 2004

Respectfully submitted,



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